CLAIMS

We claim:

1. A method of treating thrombosis in a mammal comprising administering to the mammal a pharmaceutical composition that inhibits thrombosis in the mammal, wherein the pharmaceutical composition contains a therapeutically-effective amount of a small organic compound that is potent and selective for inhibiting Factor XIa so that the differential rate of percent inhibition of thrombosis in the mammal is greater than the differential rate of percent increase in bleeding time.

2. The method of claim 1, in which the differential rate of percent inhibition of thrombosis weight in the mammal is at least 50% while the differential rate of percent increase in bleeding time is not increased or just measurably increased by less than 30%.

3. The method of claim 1, in which the small organic compound has an IC_{50} for inhibiting Factor XIa of less than 10 nM.

4. The method of claim 1, in which the small organic compound has an IC_{50} for inhibiting Factor XIa of less than 6 nM.

5. The method of claim 1, in which the small organic compound has an IC_{50} for inhibiting Factor XIa of less than 3 nM.

6. The method of claim 1, in which the small organic compound is highly selective for inhibiting Factor XIa.

7. A method of treating thrombosis in a mammal comprising administration of a small organic compound to the mammal having sufficient selectivity and potency for inhibition of Factor XIa, wherein the administration of the small molecule inhibits thrombosis in the mammal with no substantial effect on bleeding times in the mammal.

8. The method of claim 7, in which the small organic compound has an IC_{50} for inhibiting Factor XIa of less than 6 nM.

9. The method of claim 7, in which the small organic compound has an IC_{50} for inhibiting Factor XIa of less than 3 nM.

10. The method of claim 7, in which the small organic compound is highly selective for inhibiting Factor XIa.

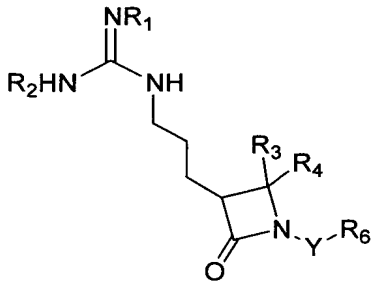
11. A method of inhibiting Factor XIa in a mammal by administration of a small organic compound with an IC_{50} for inhibiting Factor XIa of less than 120 nM.

12. The method of claim 11, wherein the small organic compound has an IC_{50} for inhibiting Factor XIa of less than 10 nM.

13. The method of claim 11, wherein the small organic compound has an IC_{50} for inhibiting Factor XIa of less than 6 nM.

14. The method of claim 11, wherein the small organic compound has an IC_{50} for inhibiting Factor XIa of less than 1 nM.

15. A method of inhibiting Factor XIa in a mammal by administration of a small organic compound having the formula (I):



(I)

wherein:

R_1 and R_2 are hydrogen;

R_3 is hydrogen or CH_3;

R_4 is selected from hydrogen, CH_3, $-CO_2R_7$, $-C(=O)NR_8R_9$, phenyl, benzyl, and phenylethyl, wherein R_7 is hydrogen, C_{1-6}alkyl, benzyl, or $-CH(OCOCH_3)CH_3$; and each R_4 group is optionally substituted with one to two R_{12};

Y is C(=O) or $-SO_2-$; wherein when Y is C(=O), then R_6 is C_{1-6}alkyl, aryl, heteroaryl, or $-NR_{10}R_{11}$, and when Y is $-SO_2-$, then R_6 is aryl or heteroaryl; and each R_6 group is optionally substituted with one to two R_{12};

R_8 and R_9 are individually selected from hydrogen and C_{1-6}alkyl, or R_8 and R_9 taken together form a five or six membered heterocyclo ring optionally substituted with one to two R_{12} and up to one R_{13};

R_{10} and R_{11} are individually selected from hydrogen, phenyl, or C_{1-6}alkyl optionally substituted with phenyl, or R_{10} and R_{11} taken together form a five or six membered heterocyclo ring optionally substituted with one to two R_{12} and up to one R_{13};

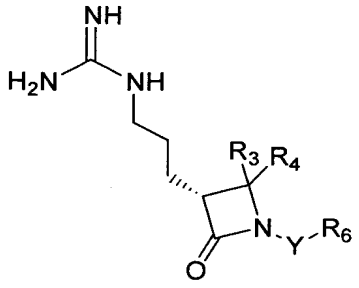
R_{12} is selected from hydrogen, halogen, trifluoromethyl, trifluoromethoxy, lower alkyl, amino, lower alkylamino, $-CO_2H$, $-CO_2$(lower alkyl), or a five or six membered saturated or unsaturated heterocyclo having up to two nitrogen heteroatoms;

R_{13} is selected from $-C(=O)(C_{1-6}$alkyl), $-CO_2(C_{1-6}$alkyl), $-C(=O)NH(C_{1-6}$alkyl), and five or six membered heterocyclo optionally substituted with one to two R_{14}; and

R_{14} is selected from hydrogen, phenyl, or C_{1-6}alkyl optionally substituted with phenyl;

or a progdrug carbamate thereof wherein at least one of R_1 and R_2 is COOR, wherein R is hydrogen, C_{1-6}alkyl, benzyl, or $CH(OCOCH_3)CH_3$, or a pharmaceutically-acceptable salt or hydrate of said compound or prodrug carbamate.

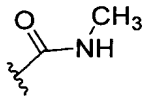
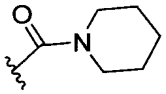
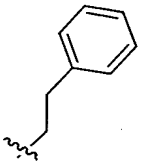
16. The method of claim 15, wherein the small organic compound has the formula (Ia):



(Ia)

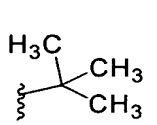
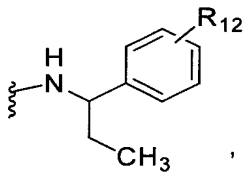
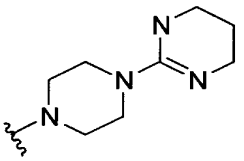
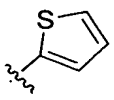
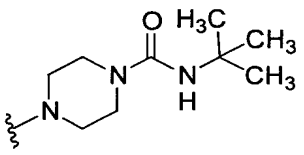
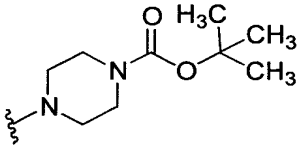
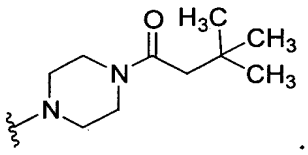
wherein:

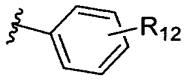
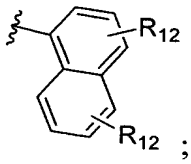
R_3 is hydrogen or CH_3;

R_4 is CH_3, CO_2H, $CO_2(C_{1-4}alkyl)$,  ,  or  ;

Y is C(=O) or $-SO_2-$; wherein:

when Y is C(=O), then R_6 is methyl, ethyl propyl,

 ,  ,  ,  ,  ,  , or  ;

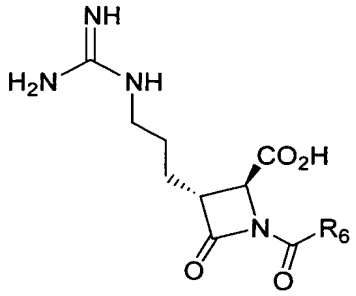
when Y is $-SO_2-$, then R_6 is selected from  ,  ;

and

R_{12} is selected from hydrogen, lower alkyl, amino, lower alkylamino, $-CO_2H$, and $-CO_2$(lower alkyl); or a progdrug carbamate thereof wherein at least one of R_1 and R_2 is -COOR, wherein R is hydrogen, C_{1-6}alkyl, benzyl, or $-CH(OCOCH_3)CH_3$, or a pharmaceutically-acceptable salt or hydrate of said compound or prodrug

carbamate; wherein the compound has an IC_{50} for inhibiting Factor XIa of less than 20 nM.

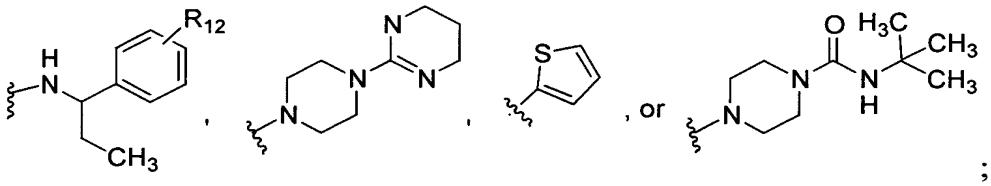
17. The method of claim 15, wherein the small organic compound has the formula (Ib),



(Ib)

wherein:

R_6 is selected from:



;

or a progdrug carbamate thereof wherein at least one of R_1 and R_2 is -COOR, wherein R_{12} is defined as above; R is hydrogen, $C_{1\text{-}6}$alkyl, benzyl, or $-CH(OCOCH_3)CH_3$, or a pharmaceutically-acceptable salt or hydrate of said compound or prodrug carbamate; wherein the compound has an IC_{50} for inhibiting Factor XIa of less than 3 nM.